REMARKS

Status of the Claims

Claims 1, 4-7 and 10-12 are pending. Claims 1, 4-7 and 10-12 are rejected. Claims 1, 4, 5, 6 and 7 are amended. No new matter is added to these claims.

Claim amendments

Claims 1 and 4-6 are amended to overcome the 35 U.S.C. §112, second paragraph rejection. Claim 1 is amended to recite modified adenoviral vector in steps (i) and (ii) of the claim and claims 4-6 are amended to recite modified adenoviral adenoviral vector to specify the adenoviral vector referred to in the claim. Claim 7 is amended to overcome the claim objections. Amended claim 7 recites an article "an" before "adenoviral vector in line 13 of the claim.

Claim Objections

The Examiner objects to claim 7 because it lacks an article "an" in front of the term "adenoviral vector" in line 13 of the claim.

Applicants have incorporated "an" in front of the term "adenoviral vector" in line 13 of claim 7. Accordingly based on these amendments, Applicants request the withdrawal of claim objections.

The 35 U.S.C. §112, Second Paragraph Rejection

Claims 1 and 4-6 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as invention. Applicants respectfully traverse this rejection.

The Examiner states that in claim 1 and its dependent claims, the term "said vector" in line 5 in step (i) and in line 11 in step (ii) renders the claims indefinite since it doesnot specify the adenoviral vector referred to in the claim. Hence, the Examiner suggests replacing the term "said vector" with "the modified adenoviral vector" to overcome this rejection. Furthermore, the Examiner states that the term "the adenoviral vector" renders claims 4-6 indefinite because it is not clear which adenoviral vector is being referred to in these claims. Hence, the Examiner suggests replacing the term "The adenoviral vector" with "The modified adenoviral vector" to overcome this rejection.

Applicants have amended claim 1 and its dependent claims as suggested by the Examiner so that the claims are no longer indefinite. Accordingly, based on this amendment and remark, Applicants respectfully request the withdrawal of rejection of claims 1 and 4-6 under 35 U.S.C. §112, second paragraph.

The 35 U.S.C. §103, Obviousness Rejection

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Sosnowski** *et al* (WO 98/40508) in view of **Muzykantov**

et al (Am J Physiol 270: L704-713, 1996). Applicants respectfully traverse this rejection.

Sosnowski *et al* disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor comprising all the elements that are taught in the instant invention except use of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody. **Muzykantov** *et al* disclose that the MAb 9B9 to angiotensin converting enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration and that MAb 9B9 is internalized by endothelial cells both in vitro and in vivo without significant intracellular degradation. The Examiner cites these teachings of the references to argue that the references combined make it obvious and motivate an ordinary skilled artisan to carry out the above modification and arrive at the instant invention with reasonable expectation of success.

The Examiner further refers to Applicants' arguments filed on 5/24/04 (pages 10-13) that were not found persuasive. In response to Applicants' lack of motivation argument, the Examiner argues that the teaching of **Sosnowski** *et al* regarding less transgene expression in the liver with FGF2-Ad was the desired and expected result for re-targeted, tropism modified adenoviral vector. Furthermore, **Sosnowski** *et al* teach that any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the

antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells. Additionally, **Muzykantov** *et al* teach that MAb 9B9 is safe, specific and useful carrier for drugs targeting specifically to pulmonary vascular endothelium after systemic administration. Since 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob, the Examiner contends that the modified retargeted adenoviral vector system of the instant invention would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing ACE and reducing transgene expression in non-pulmonary vascular endothelial cells. With regards to Applicants' doubt on success in the use of such vectors, the Examiner contends that the teachings in the references as discussed supra are sufficient to guarantee success in using such retargeted vectors.

Applicants would like to respectfully point out that although the targeting component of the modified adenoviral vector of the instant invention comprises an anti-Ad5 antibody taught by **Sosnowski** *at al* and an anti-angiotensin converting enzyme antibody taught by **Muzykantov** *et al*, these two components are linked via a bispecific antibody conjugate in the instant vector. The examples in the instant invention not only teach the construction of such a vector but also demonstrates the efficacy of the vector in vitro and in vivo. On the other hand, the references cited by the Examiner teach that the anti-Ad5 knob antibody or an anti-angiotensin converting enzyme antibody when used in adenoviral vector increased the targeting specificity of the vector and reduced transgene expression in non-targeted tissues. Despite the successful use of the

elements separately, neither of the two references have contemplated or expressed the need to combine the two different elements. Therefore, given the efficacy of the vectors disclosed by the references, one of skill in the art would not be motivated to combine the two components.

Further, although the vector taught by **Sosnowski** *et al* displayed the desired result and success and the antibody taught by **Muzykantov** *et al* was safe and specific, there is no teaching in the art regarding the use of these two components together in a vector. For instance, there is no teaching or demonstration that shows how a vector as the one disclosed in the instant invention could be constructed, whether such a vector would be stable or would be as effective, if not more effective when delivered in vivo. Therefore, even if one of skill in the art were motivated to combine the elements as per the Examiner's suggestion, one would still be trying to arrive at the instant invention. It has long been established that trying is not a standard for obviousness. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of rejections of claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. §103(a).

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Reynolds** *et al.* (Mol. Ther. 2: 562-578, 2000) in view of **Sosnowski** *et al* (WO 98/40508). Applicants respectfully traverses this rejection.

Reynolds *et al* disclose a targetable, injectable adenoviral vector for selective gene delivery to pulmonary endothelium in vivo, the vector

comprises a bispecific antibody (MAb 9B9 conjugated to 1D6.14 anti-knob Fab antibody) that target Ad infection specifically to angiotensin-converting enzyme which is preferentially expressed on pulmonary endothelium. Such a vector when injected into rats resulted in at least 20-fold increase in both Ad DNA localization and luciferase transgene expression in the lungs compared to the untargeted vector and reduced transgene expression in the liver. **Reynolds** *et al* discuss further refinements to avoid nonspecific uptake of vector for optimal efficacy. **Sosnowski** *et al* discuss use of tissue specific promoters such as endothelial-specific promoters (VEGF-receptor promoter) for expression in wide variety of cells including endothelial and smooth muscle cells to attain extra margin of specificity. The Examiner cites these teachings to argue that the references combined make the instant invention obvious and motivate an ordinary skilled artisan to arrive at the instant invention with reasonable expectation of success.

The teachings of the instant invention are as discussed supra by the Applicant. The teachings of **Reynolds** *et al* and **Sosnowski** *et al* are as discussed by the Examiner. Although **Reynolds** *et al* state further refinements to avoid non-specific uptake of vector, they do not specify the refinements. Furthermore, although **Sosnowski** *et al* teach the use of tissue specific promoters for expression in endothelial and smooth muscle cells, they do not demonstrate the use of these promoters in their constructs. Therefore, although the combined teachings of the two references may motivate one of ordinary skill in the art to use such promoters in their constructs, one may still be trying to construct the vector absent teachings of the instant invention. It has long been

established that trying is not a standard for obviousess. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of rejection of claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a).

This is intended to be a complete response to the Office Action mailed October 26, 2005. Applicants submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

Date: April 25, 2006

Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com